

REMARKS

Claims 1, 3-7, 10, 11, 14, 16, and 28-37 are pending. Claims 2, 8, 9, 12, 13, 15, and 17-27 are canceled.

Claim 1 has been amended to incorporate "in a manner sufficient to produce a stratified liquid interface between said immediately subsequent and previous liquids that moves across said surface." Support for this amendment may be found throughout the specification such as on page 29, line 32 - page 30, line 3, page 30, lines 13-16, and the originally filed Claims 9 and 15.

Claim 11 has been amended to change the dependency to Claim 1.

Claims 30-32 have been amended to recite "the angle between the plane of said flow cell and the horizontal plane of the environment." Support for this amendment may be found throughout the specification, such as on page 30, line 7.

No new matter is added by way of these amendments.

In view of the following remarks, the Examiner is requested to allow Claims 1, 3-7, 10, 11, 14, 16, and 28-37, the only claims pending and under examination in this application, after entry of the above amendments.

Rejections - 35 USC § 112

Claims 30-33 have been rejected under 35 U.S.C. 112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention.

The test for definiteness under 35 U.S.C. § 112, second paragraph, is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576; 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986).

In making this rejection, the Examiner asserts that the claims are indefinite because the claims do not define a relationship providing the angle. Without acquiescing to the correctness of the rejection, Claims 30-33 have been amended. In view of this amendment, the rejection may be withdrawn.

Rejections - 35 USC § 103 Bass '180 and Anderson

Claims 1, 3-4, 28, 34-37 are rejected under 35 U.S.C. 103(a) as being obvious over Bass et al. (USPN 6,410,180) in view of Anderson et al. (USPN 5,186,824). The Applicants traverse this rejection.

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. See, e.g., *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all elements were known in the prior art, the Office must also articulate a reason for combining the elements. See, e.g., *KSR* at 1741; *Omegallex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing *KSR*. Further, the Supreme Court in *KSR* also stated that that “a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.” *KSR* at 1740. As such, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

The rejected claims are drawn to a method for synthesizing an addressable array of at least two different polymeric ligands on a substrate. The Applicants submit that Bass '180 in view of Anderson would not lead one of skilled in the art to combine the elements in the manner suggested by the Examiner. For example, the Applicants contend that, without the hindsight provided by the Applicants, one of skilled in the art would have no reason to arrive at “displacing a previous liquid of said plurality with an immediately subsequent liquid in a manner sufficient to produce a **stratified liquid interface** between said immediately subsequent and previous liquids that moves across said surface,” as required by step (c) of Claim 1.

In making this rejection, the Examiner asserts that Bass '180 is interested in batch synthesis like the method of Anderson, and since similar reagents are used by Anderson and Bass, the combined teachings allegedly render the rejected claims obvious” (page 2 of Advisory Action dated 10/28/08). However, as explained in more detail below, one of skill in the art would have no reason to combine the elements in the manner suggested by the Examiner when the entire disclosures of the prior art references are taken into consideration.

The teaching of Bass '180 relates to a method of pulse jetting reagents onto a substrate and exposing the substrate to certain fluids in a flood station (columns 7-9). Bass also teaches that for "each of multiple addresses on the substrate, a reagent drop set is deposited during a cycle to attach a corresponding moiety for that address" (column 3, lines 29-32). However, Bass is completely silent on "displacing a previous liquid [...] with an immediately subsequent liquid," as required by the rejected claims. The Examiner then cites Anderson to remedy Bass's deficiency.

Briefly, Anderson teaches a rotor container with an inlet and outlet to introduce fluids of different density during rotation. The rotor can be used as batch reactor to synthesize oligonucleotides on controlled-pore glass beads (CPG) suspended by the fluids in the rotating rotor. As such, contrary to the assertion of the Examiner that Bass and Anderson are similar, the methods of Bass and Anderson are actually very different, the former directed to synthesizing different moiety at discrete locations on a substrate, while the latter is directed to a batch synthesis reaction, in which there can be no fabrication of different oligonucleotides on addressable locations. Accordingly, there is no reason for one of skilled in the art to combine the two references.

Moreover, based on the very different methods of Bass and Anderson, there is no support for the allegation by Examiner that Bass is also interested in batch synthesis like that of Anderson's method.

The Applicants further submit that even if the references are combined in an attempt to read onto the rejected claims as suggested by the Examiner, the proposed modification would either change the principle of operation of the methods taught by the references or render them inoperable. Under current law, such logic cannot be used to establish a *prima facie* case of obviousness.

It is well established that a reference cannot render an invention obvious

if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified...¹

or

¹ *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959); MPEP 2143.01 VI

if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose.²

The passages in Anderson cited by the Examiner in an attempt to remedy Bass's deficiency are as follows. Column 7, line 60 to column 8, line 3 teach how liquids of various density would behave in response to different centrifugal force. Figs. 2A-2D "illustrate the behavior of liquids that are introduced sequentially in increasing density to the core edge of the rotor body during rotation" (column 12, lines 28-30). Anderson further teaches that the "interface between the light solution and the dense solution assumes the configuration of a parabola of rotation" (column 12, lines 40-43). As such, Anderson teaches that the rotation of the rotor creates a parabolic interface during sequential introduction of liquids.

To follow Anderson's teachings, one of skilled in the art would resort to a rotating rotor while introducing fluids sequentially in increasing density to achieve the "stratified fluid interface," as required by Claim 1. However, combining such rotating rotor with the *in situ* fabrication of Bass in order to achieve "a stratified liquid interface [...] moves across said surface [of the array substrate]," one would end up having an addressable array inside a rotating rotor. The substrate of the addressable array may be damaged while experiencing centrifugal force inside Anderson's rotor. Since a glass bead is not an addressable array nor can an addressable array exist in suspension, it would render either Bass's method or Anderson's method inoperable.

In the Advisory Action dated 10/28/08, the Examiner asserts that there is no evidence of inoperability and that Anderson also teaches "a column at rest." In response to this assertion, the Applicants submit that the combination would render Bass's method inoperable for the following reasons. First, as described in the summary of invention and throughout the specification in Bass, reagents are jetted in a pre-determined pattern onto a substrate. Such contact printing to specific addresses on an array substrate would be inoperable if the substrate were to be enclosed and suspended in Anderson's rotating reactor.

² *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); MPEP 2143.01 V

Second, although Anderson mentions that the rotor may be used as a column at rest in one sentence in the beginning of the disclosure, the rest of the disclosure is devoted to teaching a reactor that needs to be rotated at a certain centrifugal speed during introduction of different density fluids (columns 7 and 12). As such, Anderson fails to teach any fluid displacement methods for a column at rest "in a manner sufficient to produce a stratified liquid interface [...] that moves across said surface [of the array substrate]."

Furthermore, the proposed modification would change the principle of operation of the cited references. A mounted substrate in a non-rotating flow cell would not contain the element of suspended solid-phase in a rotating chamber taught by Anderson. As for Bass, Bass's array would not comprise pulse jetting since nothing in Anderson's rotor would accommodate such contact printing onto an array. A *prima facie* case of obviousness cannot be established by completely eliminating the principles of operation of Bass or Anderson.

In addition, Applicants reiterate here that a careful consideration of the field of array synthesis reveals that the much of the teaching around the priority date of the instant application comprises drying steps in between wash steps and is completely devoid of the element of "displacing a previous liquid of said plurality with an immediately subsequent liquid" or "a stratified liquid interface [...] that moves across said surface [of the array substrate]." Numerous patents that lack these teachings have already been discussed in the response filed 10/4/08. As such, without the hindsight provided by the Applicants' application, one of skilled in the art would not have any reason to combine Bass and Anderson teachings in the manner suggested by the Examiner to arrive at the rejected claims.

In view of the foregoing discussion, the Applicants submit that the rejected claims are not obvious for at least the following reasons. First, there is no reason why one of skilled in the art would combine a batch synthesis reactor with a completely different synthesis apparatus directed to pulse-jetting an addressable array, as taught by Bass. Second, the combination of the cited references would, at best, only lead one of skilled in the art to enclose Bass's substrate in a centrifugal rotor and such an attempt to modify the teachings of the cited references to comport with the rejected claims would either render the combination inoperable or change the original principle of operations. Lastly, considering the art around the priority date

of the instant application, it is apparent that the prevalent teaching involves methods that do not displace "a previous liquid [...] with an immediately subsequent liquid" or "a stratified liquid interface [...] that moves across said surface [of the array substrate]." As such, the rejected claims are not obvious and this rejection should be withdrawn.

Rejections - 35 USC § 103 Bass '669 and Anderson

Claims 1, 3-7, 9-11, 14-16, 28, and 34-37 are rejected under 35 U.S.C. 103(a) as being obvious over Bass et al. (USPN 6,440,669) in view of Anderson et al. (USPN 5,186,824). The Applicants traverse this rejection.

As noted above, a *prima facie* case of obviousness requires the Office to articulate, *inter alia*, a reason for combining the elements.

In making this rejection, the Examiner reiterates the same reason here that one of skilled in the art would combine the cited references in a manner to comport with the rejected claims because Anderson teaches the problems of incompatible reagents. The Applicants submit for the same reasons presented above, that the combination of Bass '669 and Anderson cannot lead one of skilled in the art to arrive at the rejected claims, without the Applicants' hindsight.

Similar to Bass '180, Bass '669 teaches deposition of a plurality of oligonucleotides at discrete locations on an addressable array. On the other hand, Anderson teaches a batch synthesis reaction to generate oligonucleotides on glass beads suspended in a rotating rotor. A detailed review of the same passages cited by the Examiner in Anderson reveals that Anderson only teaches a rotating rotor to create an "interface between the light solution and the denser solution" (column 7, 8, 12, and Figs. 2A-2D). Nowhere in Anderson is there a flow cell in which an array substrate may be placed or a flow cell at rest in which there is a "stratified liquid interface [...] that moves across said surface [of the array substrate]," as required by Claim 1. As such, there is no reason for one of skilled in the art to combine an *in situ* fabrication process of Bass '669 with a batch synthesis reactor of Anderson.

Furthermore, as discussed previously, even if they were to be combined, the combination would either render Bass's or Anderson's methods inoperable or completely change their principles of operation. Such logic is not permitted in establishing a *prima facie* case of obviousness.

Lastly, the art of array synthesis around the time of filing only teaches drying steps between exposures to different fluids. In view of such prevalent practice of array synthesis, there can be no reason to lead one of skilled in the art to combine Bass and Anderson in the manner suggested by the Examiner.

In addition to the fact that Anderson cannot remedy Bass's deficiency for not teaching or suggesting step c) of Claim 1 and that all claim rejections should be withdrawn for this reason alone, the Applicants further note that the combination of Bass and Anderson also does not teach or suggest the following dependent claims.

With respect to Claim 10, neither Anderson nor Bass teaches or suggests the flow rate of the fluid to "range from about 1 cm/s to about 20 cm/s." In making this rejection, the Examiner cites column 5, lines 25-27 and column 14, lines 44-53 in Anderson as allegedly teaching that it is important to control flow rate and as such, one of skilled in the art would have been motivated to adjust the flow rate. The Applicants traverse this rejection of Claim 10.

A detailed review of the cited passages reveal that Anderson provides the teachings set forth in the following, none of which is related to a flow rate of "about 1 cm/s to about 20 cm/s." Column 5, lines 15-27 teaches valves to control fluid flow. Column 14 teaches density sensors to ensure that the density of the incoming fluid is of the right density.

In view of the above, the Examiner's assertion that Anderson teaches the importance of **flow rate** is unsupported. Nowhere is there a teaching or suggestion relating to flow rate. As such, the Examiner fails to articulate any reasoning that would have prompted one of skilled in the art to arrive at the flow rate ranging "from about 1 cm/s to about 20 cm/s." Withdrawal of the rejection of Claim 10 is respectfully requested.

With respect to Claim 11, the Applicants contend that neither Bass nor Anderson teaches or suggests "sensing movement of the stratified fluid interface." In making this rejection, the Examiner points to column 12, lines 28-67 and Figs. 2A-2D in Anderson. The Applicants submit that the cited passages only "illustrate the behavior of liquids that are introduced sequentially in increasing density [...] during rotation" (Column 12 and Figs. 2A-2D). These passages are completely silent on "sensing movement of the stratified fluid interface." Since no teaching or suggestion is found anywhere in the cited references, rejection of Claim 11 should be withdrawn.

Rejections - 35 USC § 103 Bass '669, Anderson, and Goldberg

Claims 29-33 have been rejected under 35 U.S.C. 103(a) as allegedly obvious over Bass et al. (USPN 6,440,669) in view of Anderson et al. (USPN 5,186,824), in further view of Goldberg (USPN 5,959,098). The Applicants traverse this rejection.

In making this rejection, the Examiner acknowledges that Bass and Anderson do not teach “plane of the flow cell or environment” and cites Goldberg in an attempt to remedy the deficiency of Bass and Anderson.

As noted above, Bass and Anderson cannot be used to establish a *prima facie* case of obviousness because the combination of the two methods would either render Bass's method or Anderson's method inoperable or change their principles of operation. Moreover, popular array synthesis methods around the time of filing are completely silent on “displacing a previous liquid [...] with an immediately subsequent liquid” and a “stratified liquid interface [...] that moves across said surface [of the array substrate].” Rather, the prevalent practice demonstrated by various patents resorts to air-drying. As such, there is no reason for one of skilled in the art to combine the elements from Bass and Anderson in the manner suggested by the Examiner without the hindsight provided by the Applicants.

Since Goldberg is cited solely for the alleged teaching of a flow cell in vertical alignment, Goldberg cannot remedy the deficiency of Bass and Anderson discussed above. As such, the Applicants respectfully request the withdrawal of this rejection.

As such, it is believed that the rejection may be withdrawn and that all of the claims are allowable.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Bret Field at (650) 327-3400.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10040506-1.

Respectfully submitted,

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